Enabling Optimized Preclinical Modeling: A US National Roadmap and Resource

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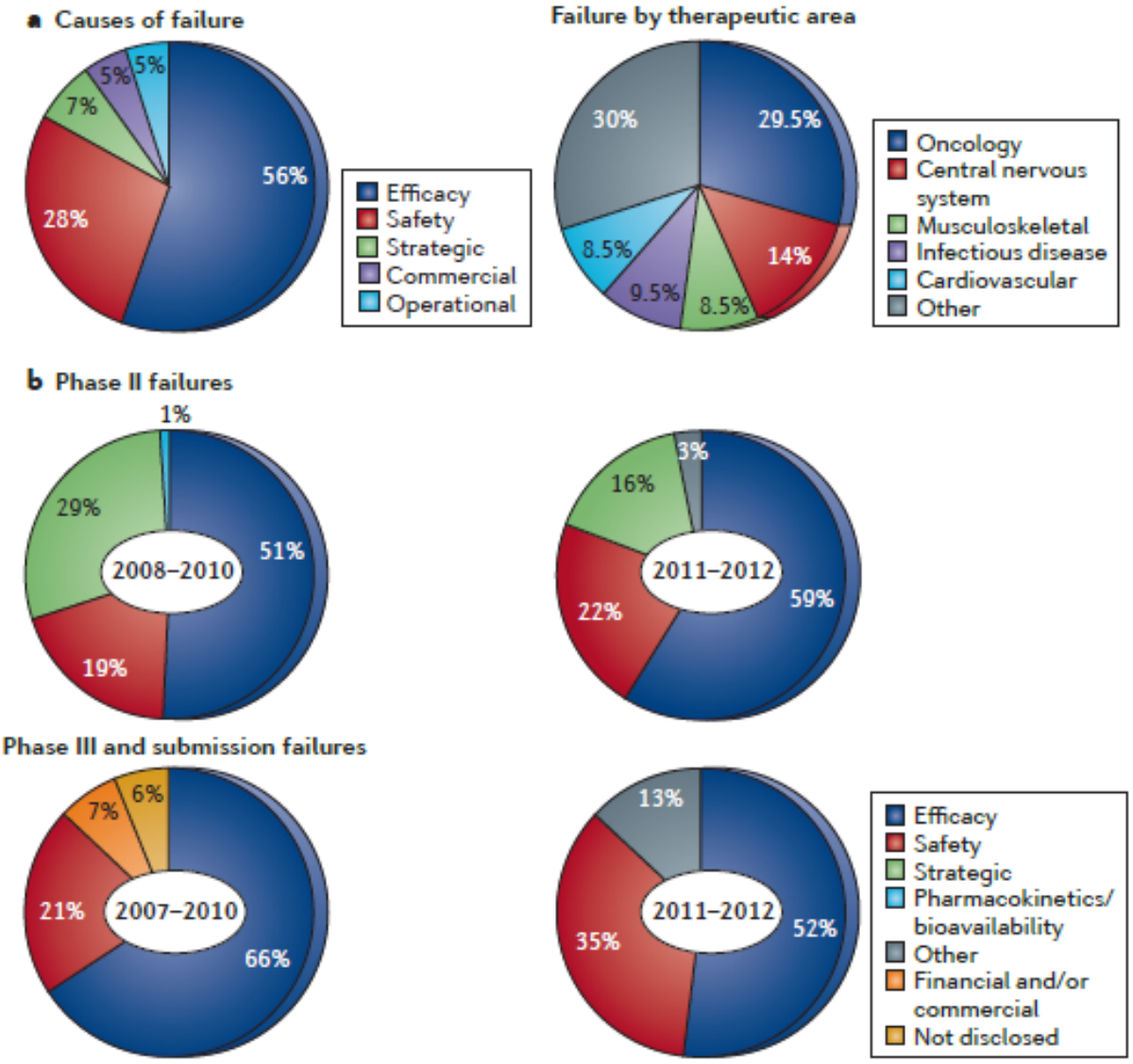
GSK R&D

Contemporary drug development is an unsustainable model

Phase II and Phase III attrition rates 2011–2012

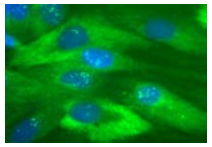
Cost of development = $1.2-2.6B/drug



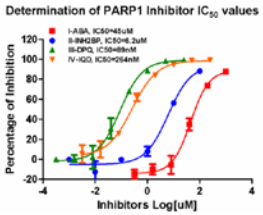
Current approaches to drug development

Capabilities

Bioinformatics



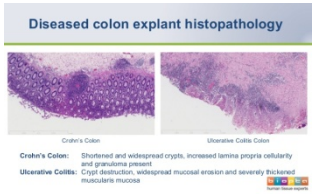
Phenotypic assays



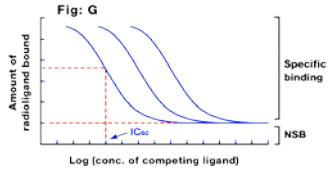
Activity assays

Animal studies

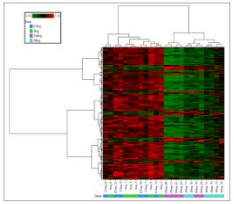
Patient studies



Human tissue



Binding assays



-omics

Target ID & validation → it/lead scovery → Lead optimisation → Candidate selection → Preclinical safety → Clinical assessment

#compounds	1000's	100's	10's	1-3

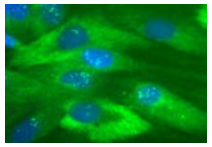
Evidence building

Targets that modulate disease + Compounds that bind targets + Compounds that are active at the target + Compounds that are bio-available + Compounds that are safe

Current approaches to drug development

Capabilities

Bioinformatics



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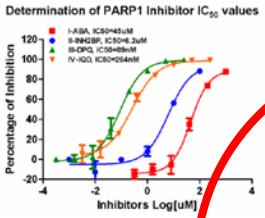
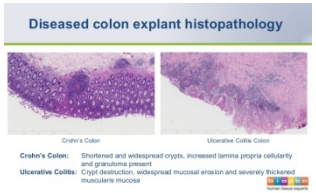


Activity assays



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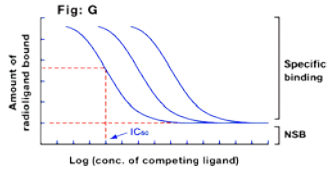
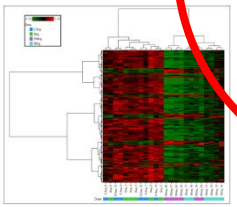


Binding assays



-omics

Animal studies

Patient studies

Target ID & validation	Hit/lead discovery	Lead optimisation	Candidate selection	Preclinical safety	Clinical assessment
#compounds	1000's	100's	10's	1-3	

Animal models are an important and influential platform

Evidence building

Targets that modulate disease + Compounds that bind targets + Compounds that are active at the target + Compounds that are bio-available + Compounds that are safe

Some believe that platform to be a problem!

Genomic responses in mouse models poorly mimic human inflammatory diseases

www.pnas.org/cgi/doi/10.1073/pnas.1222878110

Although there is no direct evidence of a causal relationship, it is likely that the recurrent failure of apparently promising interventions to improve outcome in clinical trials has in part been caused by inadequate internal and external validity of preclinical studies and publication bias favouring positive studies. On

OPEN ACCESS Freely available online

PLoS MEDICINE

Research in Translation

Can Animal Models of Disease Reliably Inform Human Studies?

H. Bart van der Worp[1]*, David W. Howells[2], Emily S. Sena[2,3], Michelle J. Porritt[2], Sarah Rewell[2], Victoria O'Collins[2], Malcolm R. Macleod[3]

1 Department of Neurology, Rudolf Magnus Institute of Neuroscience, University Medical Centre Utrecht, Utrecht, The Netherlands, 2 National Stroke Research Institute & University of Melbourne Department of Medicine, Austin Health, Melbourne, Australia, 3 Department of Clinical Neurosciences, University of Edinburgh, Edinburgh, United Kingdom

Regulatory Toxicology and Pharmacology 64 (2012) 345–349

Contents lists available at SciVerse ScienceDirect

Regulatory Toxicology and Pharmacology

journal homepage: www.elsevier.com/locate/yrtph

The ability of animal studies to detect serious post marketing adverse events is limited

Peter J.K. van Meer [a,*], Marlous Kooijman [b], Christine C. Gispen-de Wied [c], Ellen H.M. Moors [b], Huub Schellekens [a,b]

Two primary areas of critique:

- translational relevance
- methodologic reproducibility

Efforts to fix those problems are emerging

NC3Rs

National Centre for the Replacement, Refinement and Reduction of Animals in Research

The ARRIVE guidelines
Animal Research: Reporting *In Vivo* Experiments

Carol Kilkenny[1], William J Browne[2], Innes C Cuthill[3], Michael Emerson[4] and Douglas G Altman[5]

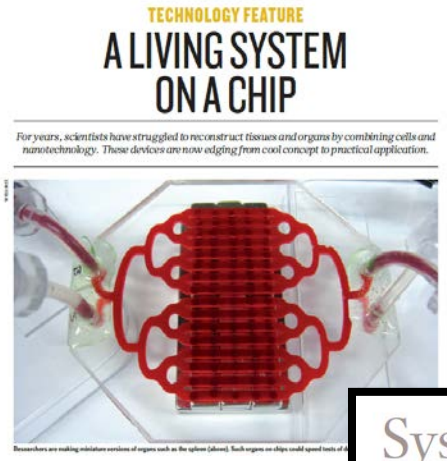
Originally published in PLoS Biology, June 2010[1]

NIH plans to enhance reproducibility

Francis S. Collins and **Lawrence A. Tabak** discuss initiatives that the US National Institutes of Health is exploring to restore the self-correcting nature of preclinical research.

612 | NATURE | VOL 505 | 30 JANUARY 2014

Lots of new opportunity!

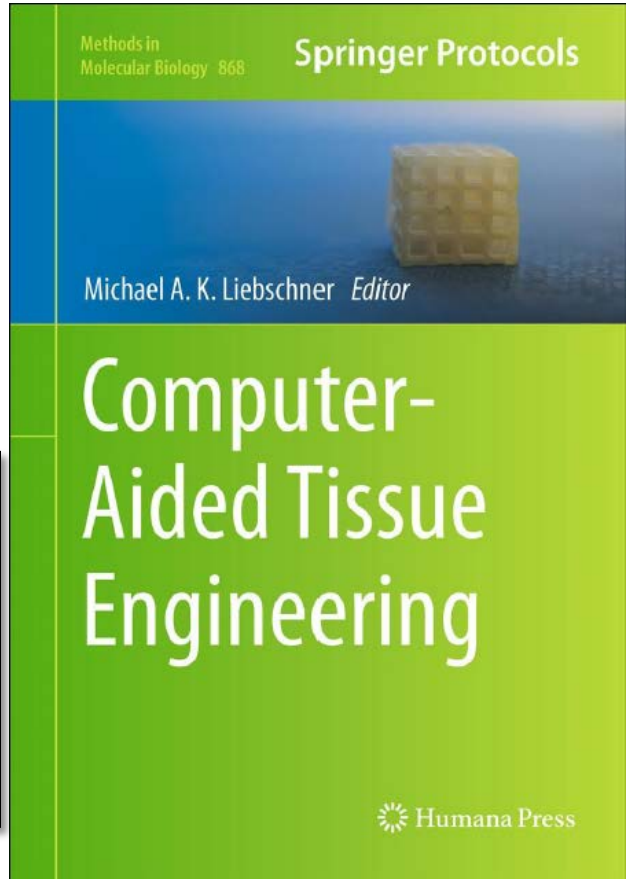

TECHNOLOGY FEATURE

A LIVING SYSTEM ON A CHIP

For years, scientists have struggled to reconstruct tissues and organs by combining cells and nanotechnology. These devices are now edging from cool concept to practical application.

Systems Pharmacology to Predict Drug Toxicity: Integration Across Levels of Biological Organization*

Jane P.F. Bai and Darrell R. Abernethy



ASSOCIATE EDITOR: ERIC L. BARKER

Computational Methods in Drug Discovery

Gregory Sliwoski, Sandeepkumar Kothiwale, Jens Meiler, and Edward W. Lowe, Jr.

Meiler Laboratory, Center for Structure Biology, Vanderbilt University, Nashville, Tennessee

Lots of public resource!

Sutherland *et al. Stem Cell Research & Therapy* 2013, 4(Suppl 1):I1
http://stemcellres.com/content/4/S1/I1

INTRODUCTION Open Access

$70M

The National Institutes of Health Microphysiological Systems Program focuses on a critical challenge in the drug discovery pipeline

Margaret L Sutherland*[1], Kristin M Fabre*[2] and Danilo A Tagle[2]

systems for a 4-week period. Like the NIH MPS Program, the DARPA Program represents a 5-year, $75 million commitment.

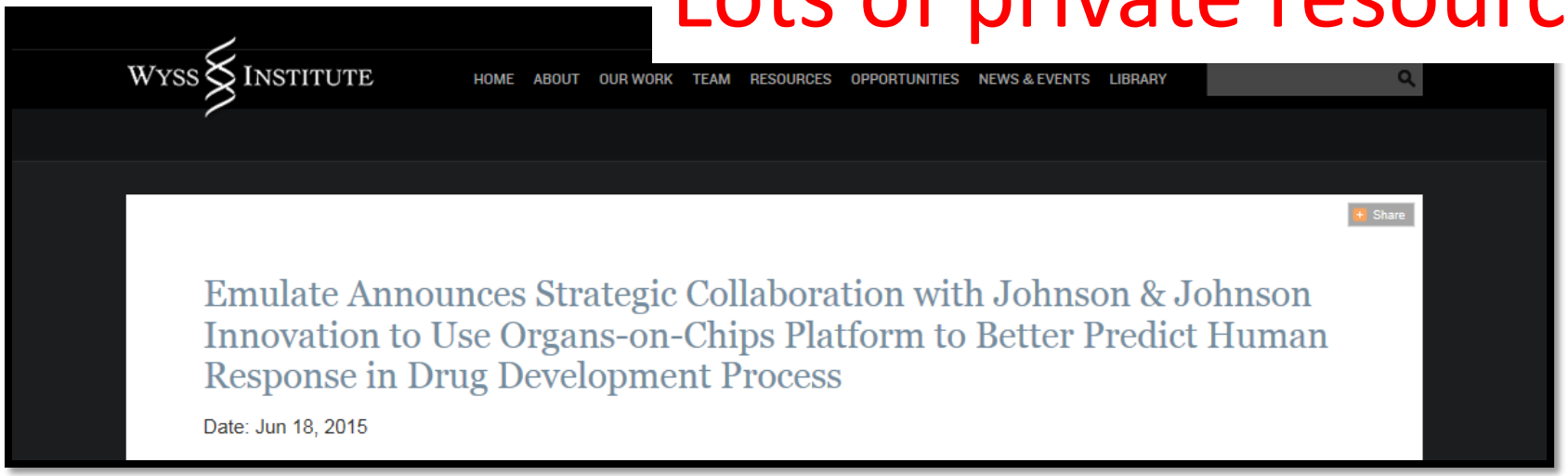
$75M

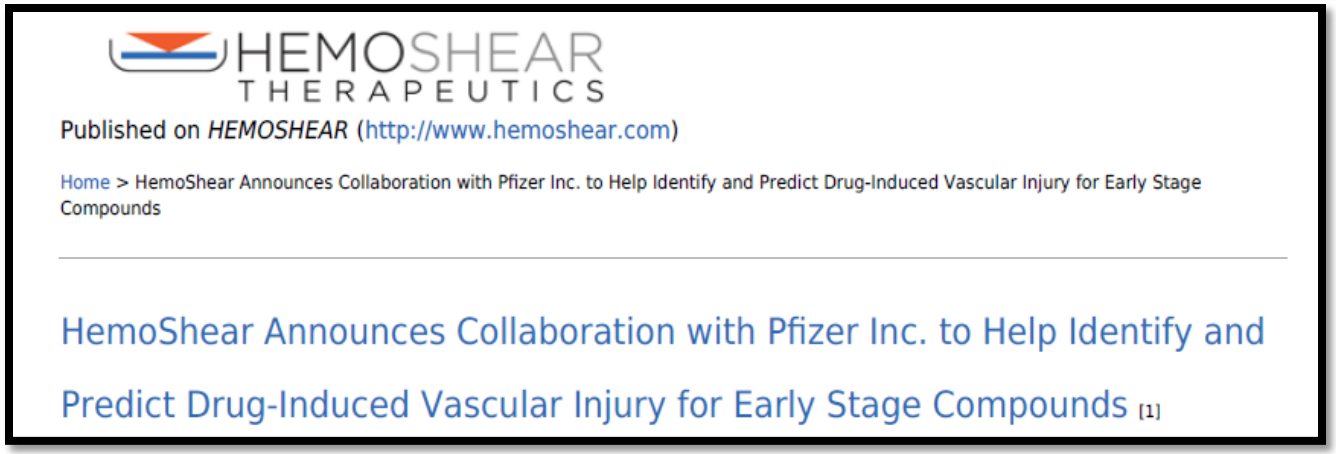
In Vitro Screening of Environmental Chemicals for Targeted Testing Prioritization: The ToxCast Project

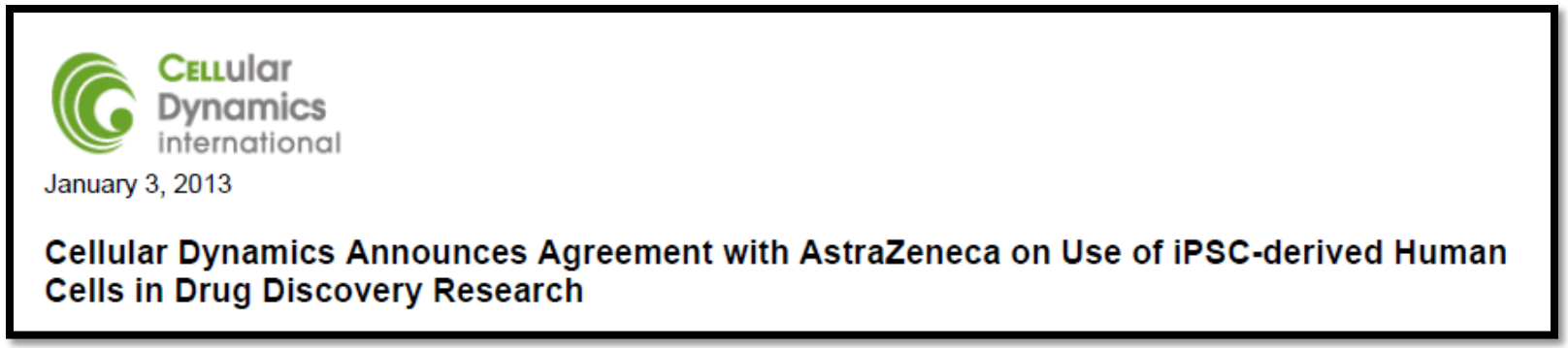
Richard S. Judson, Keith A. Houck, Robert J. Kavlock, Thomas B. Knudsen, Matthew T. Martin, Holly M. Mortensen, David M. Reif, Daniel M. Rotroff, Imran Shah, Ann M. Richard, and David J. Dix

National Center for Computational Toxicology, Office of Research and Development, U.S. Environmental Protection Agency, Research Triangle Park, North Carolina, USA

Lots of private resource!







Without a strategy, are those resources being used efficiently?

A Proposal

Aim- improve the predictivity of our non-clinical modeling strategies and reduce our dependence on animals

Elements

- Develop a national, multi-sector strategy for supporting and industrializing innovative, non-animal technologies
- Develop incubators that facilitate the integration and industrialization of novel capabilities
- Align the technologies to real world challenges
- Pool public-private resources